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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| UNDERDAHL, THANE E | |

| ART UNIT | PAPER NUMBER |
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| 1651 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/826,585 | O'HARA ET AL. | |
| | Examiner | Art Unit | |
| | Thane Underdahl | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6,8,9,13-15,17,20,23-26 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9,13-15,17,20,23-26 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

**Response to Restriction/Election**

Applicant's response to the species election without traverse filed on 4/18/07 the applicant cancelled non-elected claims and species.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8, 9, 13-15, 17, 20, 23-26, 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are drawn to a method where one step is "obtaining a fluid sample from a test subject". While indeed a fluid can be a liquid, but can also be defined as a gas or plasma. It is clear that cytoplasmic biomolecules cannot be obtained from most gasses or plasma. Clarification is required. This rejection is easily overcome by replacing fluid with liquid or bodily fluid.

Furthermore claim 13 and its dependants indefinite because it states that the "releasing of said cytoplasmic biomolecules involves macromolecular complexes formed after exposure to the stabilizing agent". This is confusing since claim 13 depends from claim 8 which limits that the stabilizing agent is added in step a) of claim 1. Step a) is before the releasing of the biomolecules of step b) and thus it is unclear how the stabilization agent creates macromolecular complexes that release biomolecules when it is included in the step of obtaining the liquid sample not lysing the cells of the sample. Clarification is required.

Also claim 17 is indefinite since it lacks antecedent basis from the claims from which in depends. It contains the phrase "nucleophiles". A term which is nowhere else to be found in the claims. The examiner believes this word is to be enzymes since that puts the claim in closer relationship to claim 15. In the interest of compact prosecution, claim 17 will read "The method of claim 15, where the enzyme buffers are from a group consisting of phosphate-based buffers, tris-buffers, acetic hydrazide, hydroxylamine, and combinations thereof".

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8, 13, 20, 23, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmitz et al. (U.S. Patent # 6,190,870).

These claims are drawn to a method for extracting intact cytoplasmic biomolecules from cells comprising the steps of :

a) obtaining a liquid sample from a test same from a subject that is a mixture of cell populations

b) releasing said cytoplasmic biomolecules from said cells

c) isolating said cytoplasmic biomolecules and

d) analyzing said cytoplasmic biomolecules.

The method is further limited by stating the liquid sample is whole blood . The target cells are selected by immunomagnetic selection. The samples are treated with a cell stabilization agent that once exposed forms macromolecular complexes. The cytoplasmic biomolecules being isolated are nucleic acids, specifically RNA. Also the target cells above are analyzed via phenotypic expression such as morphological examining.

Schmitz et al. teach a method that obtains a sample of blood from a test subject (see Abstract) and isolates the cells by immunomagnetic separation (see Abstract). The sample is exposed to a anticoagulant that stabilized the blood sample to keep the cells (macromolecular complexes) separated and prevent clotting. The anticoagulant also allows Schmitz et al. to prepare leukocyte rich buffy coats (macromolecular complexes) (col 10, lines 5-10). They continue to teach that tumor cells may have their RNA isolated and analyzed by PCR or competitive hybridization (col 9, lines 4-5). These analysis techniques inherently mean the RNA must be released and isolated from the cell. Furthermore Schmitz et al. teach that tumor cells can be assessed by morphological examination (col 8, lines 60-61). Therefore the reference anticipates claims 1-3, 8, 13, 20, 23, 25 and 26.

Claims 1, 8, 13, 14, 15, 17, 20, 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Kearney et al. (U.S. Patent # 5,589,335).

The description of claims 1, 8, 13, 20, and 23 are listed in the 35 U.S.C § 102(b) rejection above. Claim 14 and 15 limit that the cytoplasmic biomolecules from said cells are release by enzymatic digestions such as that from proteinase K. Claim 17 limits that the buffers for the enzyme of which include phosphate-based buffers. Claim 24 limits that the nucleic acids are isolated using magnetic beads.

Kearney et al. teach a method for isolating RNA using magnetic oligo(dT) magnetic beads (col 37, V. TMA.TFA and col 17, Protocol for Hybridization and Elution/Recapture). Kearney obtains a liquid sample of *E. coli* and *Listeria monocytogenes* and lyses them with Proteinase K in a phosphate buffered solutions to isolate their RNA for hybridization studies (col 37, V. TMA.TFA and col 17, Protocol for Hybridization and Elution/Recapture and col 8 Glossary). These cells are listed by Kearney as a concentration so are inherently in some liquid media that stabilizes them and as such the cells are free floating macromolecular complexes in the stabilization agent. Therefore the reference anticipates claims 1, 8, 13, 14, 15, 17, 20, 23 and 24.

Claims 1, 2, 4, 8, 9, 13, 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Valladeau et al. (U.S. Patent # 6,277,959) as supported by Chirgwin et al. (Biochemistry, 1978) and QIAGEN (OLIGOTEX Handbook).

The description of claims 1, 2, 4, 8, 13, 20-23 are listed in the 35 U.S.C § 102(b) rejection above. Claim 9 limits that the stabilizing agent of claim 8 is an aldehyde.

Valladeau et al. teach a method of isolation of RNA from blood cells (Valladeau, col 45, line 18 to col 46 line 23). The selected cells (macromolecular complexes) are

cultured and stabilized with paraformaldehyde (Valladeau, col 54, lines 20-25). Valladeau then uses a procedure presented by Chirgwin et al. to lyse the cells (Chirgwin, page 5295, col 1) which includes a guanidinium thiocyanate stock solution that contains the surfactant N-lauroylsarcosine, to lyse the cells (Chirgwin, page 5294. The RNA is isolated with the OLIGOTEX mRNA isolation kit from QIAGEN (OLIGOTEX Handbook page 12-14).

Therefore the reference anticipates claims 1, 2, 4, 8, 9, 13, 20-23.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8, 9, 20, 23, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmitz et al. as applied to 1-3, 20, 23, 25 and 26 above and for further view of Hyde (Protocols in Molecular Parasitology, 1993).

The description and rejection of claims 1-6, 8, 9, 20, 23, 25 and 26 are listed in the 35 U.S.C § 102(b) rejection above. Claims 3-6 limit that the cytoplasmic biomolecules are released by the addition of a permeabilizing agent. This permeabilizing agent is selected from a group consisting of a detergent, surfactant, and a combination thereof. Most specifically the permeabilizing agent is saponin. Claims 8 and 9 limit that a stabilizing agent such as formaldehyde is applied to the liquid sample.

While Schmitz et al. does teach that saponin is a permeabilizing agent (col 6, lines 58-62) that forms pores in the cell membrane (col 5, lines 20-25) and does use it to lyse Erythrocytes (Example 1) they do not specifically teach the use of saponin to lyse the cells for the extraction and isolation of RNA. However they also include saponin with other permeabilizing agents such as Triton X-100 and NP-40 which are readily known in the art to be excellent detergents for use in cell lysis buffer. Furthermore Hyde et al. teach that saponin is used in lysis buffers to extract RNA from blood cells. It would have been obvious to someone skilled in the art to use saponin to lyse blood cells (Hyde, page 134-135). The motivation is provided by Schmitz et al. who already use saponin containing buffers to lyse erythrocytes and the reasonable expectation of success is provided by Hyde who teaches the method to use saponin to successfully lyse blood cells.

Claims 1, 2, 4, 8, 9, 13, 20-23 and 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Valladeau et al. as applied to claims 1, 2, 4, 8, 9, 13, and 20-23 and for further reasons listed below.

The description and rejection of claims 1, 2, 4, 8, 9, 13, 20-23 are listed in the 35 U.S.C § 102(b) rejection above. Claim 31 is drawn to analyzing the cytoplasmic RNA with two genetic markers by multi-gene RT-PCR.

While Valladeau teach the use of RT-PCR to assess the expression of the protein DCMP1 (col 48, lines 31-45) they do not teach a multi-gene approach. However, Valladeau et al. teach that other DC-type proteins can be analyzed by PCR

probes (col 23, lines 40-55). It would have been obvious to someone skilled in the art to use multiple probes to analyze DC-type proteins of tumor cells. The motivation comes from Valladeau et al. who teach that multiple DC-type proteins can be analyzed by PCR probes and the reasonable expectation of success also comes from Valladeau et al. who already successfully performed RT-PCR analysis on DCMP1. Furthermore, the art is replete with instances and instruments capable for multi-gene PCR analysis. Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1, 2, 4, 8, 9, 13, 20-23 and 31 are not allowable.

In summary no claims, as written, are allowed for this application.

**In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure**, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571)

272-9042. The examiner can normally be reached during regular business hours, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1651

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